

# Implications of Aquatic Animal Health for Human Health

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Human health and aquatic animal health are organically related at three distinct interfaces. Aquatic animals serve as important contributors to the nutritional protein, lipid, and vitamin requirements of humans; as carriers and transmitters of many infectious and parasitic diseases to which humans are susceptible; and as indicators of toxic and carcinogenic substances that they can convey, in some part, from aquatic environments to man and other terrestrial animals. Transcending these relationships, but less visible and definable to many, is the role that aquatic animals play in the sustenance of our integrated planetary ecosystem. Up to the present, this ecosystem has been compatible with mankind's occupation of a niche within it at high but ultimately limited population levels. In the past century we have become clearly aware that human activities, particularly over-harvesting of aquatic animals together with chemical degradation of their habitats, can quite rapidly lead to perturbances that drastically shift aquatic ecosystems toward conditions of low productivity and impaired function as one of earth's vital organs.

The negative values of aquatic animals as disease vectors are far outweighed by their positive values as nutritional sources and as sustainers of a relatively stable equilibrium in the global ecosystem. In the immediate future we can expect to see increased and improved monitoring of aquatic habitats to determine the extent to which aquatic animals cycle anthropogenic toxic and carcinogenic chemicals back to human consumers. In the long term, methods are particularly needed to assess the effects of these pollutants on reproductive success in aquatic communities and in human communities as well. As inputs of habitat-degrading substances change in quality and quantity, it becomes increasingly urgent to evaluate the consequences in advance, not in retrospect. A new, more realistic and comprehensive philosophy regarding aquatic environmental preservation and equally new and comprehensive technological advances reflective of this philosophy will be required. In the next century we will see a serious test of whether or not mankind has lost its ability to foresee and forestall the side effects of scientific and technological ingenuity.

## Introduction

Being a terrestrial animal, humankind has tended to find its most frequent environmental interactions with those parts of earth and her biota that lie above the surface of earth's waters. In the past half century, with great technological advances in many areas including submarine exploration, we have come to realize more fully the close and vital intimacy that exists between ourselves and the aqueous portion of our environment. Relationships between aquatic animal health and human health have several important facets, that are listed as follows.

## Nutritional

Aquatic animals are, and have been for as long as written history and archaeological evidences go back, a large component of human nutritional supplies, particularly with respect to the protein component. Preferential colonization patterns of modern as well as of primitive peoples adjacent to rivers, lakes, and marine waters are in part a reflection of this fact. Feral aquatic animal

populations are now the last resource of large magnitude left to the hunter-providers of human foods, as opposed to the resources stemming from the agrarian-providers. Aquaculture, following the pattern developed in agriculture over millennia, is becoming increasingly important, and modern transportation methods are tending to even out the distribution of aquatic foods so that relative consumption rates have risen in inland populations. It has recently been estimated that the average Japanese consumes about 90 g of fishery products per day, or five times the amount the average American consumes (1). As well, there is an area of interrelationship between agricultural food products and captured aquatic foods, in that fish meals form a sizeable part of diets fed to poultry and mammalian meat animals. This has the effect of further increasing man's dependency on aquatic food sources. The nutritional interface between aquatic animal health and human health is a most important one, and is likely to increase in importance for some time, although this prediction rests, as will be clarified, on troubled waters.

## Infectious and Parasitic Diseases

Some viral, bacterial, and protozoan and metazoan

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parasitic diseases are shared by aquatic animals and man and can be transmitted to humans or sometimes cycled from human to aquatic animal and back again. Textbook examples are the several types of schistosomiasis, transmitted through freshwater snails that act as intermediate hosts; paragonimiasis (lung fluke disease), transmitted through first a snail, then a crustacean; and infestation by a fish tapeworm, *Diphylllobothrium latum*, transmitted directly through eating raw fish. Schistosomiasis is the most serious disease of this group, with some 200 million persons estimated to be infected in the many parts of the globe where it is endemic, and some 500 to 600 million persons estimated to be at high risk of becoming infected (2). Infection with the *Hematobium* species is often accompanied late in the disease by urinary bladder cancer. Recent advances in chemotherapy of schistosomiasis have been successful within limited localities, and the prospects of more general control appear to be good.

A number of bacterial and viral disease agents are transmitted through ingestion of uncooked or inadequately cooked aquatic foods, even though the relevant animals are only carriers and are themselves unaffected by the agents in this category. Examples are viral hepatitis, the several gram-negative bacterial enteritides such as salmonellosis, typhoid fever, and cholera, acute rotaviral gastroenteritis (Norwalk agent infection), gastroenteritis caused by *Vibrio parahaemolyticus*, and possibly even poliomyelitis. Important though they are in some geographic areas and to the individuals afflicted with them, the known diseases in this category are now mostly well understood, can be prevented and/or treated with available procedures, and do not appear to be on the increase, except for cholera and viral gastroenteritis in areas where human fecal contamination of waters escapes control.

### Aquatic Food Animals As Indicators or Conveyors of Cytotoxic and Carcinogenic Chemicals

Many fishes, e.g., several species of puffers, normally carry highly potent neurotoxins (tetrodotoxin in the case of the puffers) in their viscera, skin, and roe (3). While the muscle of these fishes contains little or none of the toxin, the muscle can become contaminated by contact with or diffusion from the viscera or skin, and the consumer may become severely ill or die in a paralytic state. Such unhappy events are rare, however, and do not represent a major problem in public health in the United States, although they do in some oriental countries including Japan and China.

Certain dinoflagellates such as *Gonyaulax* and *Gymnodinium* spp. and an increasing number of others are known to synthesize neurotoxins (saxitoxin, ciguatera toxin, maitotoxin), and during a bloom (red or brown tide) filter-feeding bivalve molluscs can fill their alimentary tracts with these poisonous organisms (4). If the molluscs, particularly mussels, clams, scallops, cockles,

and oysters are then ingested by humans, other mammals, birds, or fish, severe acute muscle paralysis and death can ensue. These acute intoxications are not strictly related to the health of the consumed animal, but rather to the health of the ecosystem in which it lives. Consumption of animals from such perturbed ecosystems can be avoided and is prevented most of the time by educational steps and advisories to the public from fisheries and public health agencies. It is currently perceived by some, however, that red tides are on the increase, possibly as a result of nutrient enrichment of estuarine and coastal waters by inorganic fertilizer run-offs and increased sewage inputs (1,5,6). If so, the availability of edible molluscs may be curtailed beyond the extensive curtailments already in effect through closings of shellfish beds because of contamination with excessive numbers of fecal coliform bacilli.

Aquatic animals whose habitats or food webs have been contaminated by xenobiotic toxic chemicals of many sorts may, through the pathological effects of the chemicals, serve as indicators of those chemicals in the environment [(7-11) for conference volumes on this subject]. With or without pathological effects demonstrable by standard morphological methods, the animals that contain these chemicals can convey them to human and other predators. Perhaps the most dramatic verifications of the latter statement are the epidemics of Minimata disease (mercury poisoning) and *itai-itai* disease (cadmium poisoning) that occurred in Japan in the 1950s among consumers of aquatic animals [see (1) and (12) for early studies]. Constant monitoring for trace metal contamination of fish and shellfish has ensued (13-18) and repetitions of similar major epidemics have largely been avoided, although trace metal contamination of many estuarine environments is still recognized as an ever-present threat.

During the past 25 years an at-first slow, but now much accelerated build-up of evidence has developed, supporting the notion that some neoplasms in feral fishes and molluscs are indicators of carcinogens in aquatic environments. Hepatic neoplasms are currently receiving the most attention. In retrospect, it seems probable that the oral and cutaneous papillomas, described by Lucke' and Schlumberger in large numbers of brown bullhead from the Delaware and Schuylkill Rivers near Philadelphia, were related to environmental contaminants as early as 1941 (19). Schlumberger speculated on this possible relationship in 1957 (20). In that same year, Russell and Kotin suggested chemical pollutants as the cause of lip papillomas in white croakers from Santa Monica Bay, CA (21).

Despite the accumulating evidence, Mix, as recently as 1986, raised serious questions and criticisms regarding many of the studies relating elevated prevalences of neoplasms to chemical contamination of environments (22). Many of these criticisms were justifiable, particularly those directed toward studies of molluscan neoplasms, and they properly indicate a need to tighten up in the design, conduct, and interpretation of surveys

in the future. However, with respect to certain neoplasms in fishes, the evidence now seems compelling that there is a strong association between elevated prevalences of neoplasms and habitat contamination. The problem is no longer whether the habitats are contaminated, or whether the neoplastic prevalences are real, or whether the associations are valid compared with control populations in uncontaminated waters. The problem is that known carcinogenic contaminants are present in such large variety that, thus far, it has not been possible to determine which carcinogen(s) or which combinations of carcinogens and/or promoters are responsible for the neoplasms that occur in fishes in each respective habitat.

Three features of enzootic neoplasms in fishes stand out and offer leads that are being followed in investigations aimed toward identifying the cause(s): a) the enzootics are almost invariably found in fish populations in

waters receiving large inputs of wastes from urban-industrialized communities; b) the most common organ sites in which neoplasms occur are the liver, an organ on which the organism heavily depends for many detoxification processes, and the skin, an organ directly and constantly in contact with the aqueous environment and frequently in contact with bottom sediments; c) most, but not all of the hepatic neoplasms in known enzootics among feral fishes have been found in bottom-feeding species, signifying that carcinogens probably reach bottom-feeders preferentially by adsorption to sediments and detritus, which are then ingested by zooplankton and adult invertebrates, which in turn are ingested by the bottom-feeding fishes, resulting in bioconcentration and movement of the carcinogens upward through trophic levels. Table 1 presents the chronology and main features of the discoveries of clusters and enzootics of

Table 1. Feral fishes with hepatic neoplasms in the U.S.<sup>a,b</sup>

Common name	Location	Prevalence	Histotype	Supporting chemical data	References
White sucker	Deep Creek Lake, MD	25% (3/12)	Cholang	0 (presumably PAHs and CHIPs)	(23)
Brown bullhead	Deep Creek Lake, MD	1% (1/100)	Hep	0 (presumably PAHs and CHIPs)	(23)
White sucker	Pleasant Valley Lake, MD	6% (1/17)	Cholang	0 (presumably CHIPs)	(24)
Brown bullhead	Fox River, IL	12–13% (74/567)	Hep	Carcinogens, other organic chemicals in water	(25,26)
Brown bullhead	Lake of the Woods, Canada (reference site)	1–2% (3/188)	Hep	Clean by chemical analysis	(25,26)
English sole, other pleuronectids, Pacific tomcod, staghorn sculpin	Puget Sound, WA (9 sites)	Up to 24% for English sole N = 1318	Hep, cholang, mixed	PAHs, PCBs, CHIPs, many others; PAH metabolites in bile	(27–29) (28,29)
Atlantic tomcod	Hudson River, NY	25% (66/264)	Hep	PCBs in liver, other tissues	(30,31)
Brown bullhead	Black River, OH	Up to 38% (48/125)	Hep, cholang	PAHs in sediment, tissues	(32,33)
Sauger and walleye <sup>c</sup>	Torch Lake, MI	100% (3/3) 27% (3/11)	Hep	0 (history of copper mine wastes and flotation oils)	(34)
Brown bullhead, redhorse sucker and drum	L. Erie, MI Niagara River, NY	NNS	Hep, cholang, carcinoma	PAHs in sediment	(35)
Brown bullhead	Buffalo River, NY	17% (5/28)	Hep, cholang, carcinoma	PAHs in sediment, tissues	(36)
Winter flounder	Boston Harbor, MA	8% (16/200)	Hep, cholang	PCBs, PAHs in previous studies	(37) (38,39)
Winter flounder	Salem Harbor, MA	5% (4/74)	Hep, cholang	0 (near sewage outfall)	(40)
White perch <sup>c</sup>	Chesapeake Bay, MD	5–10% NNS	Hep, cholang	0	(41)
Oyster toadfish	York River, VA	10% (1/10)	Hep	0 (refinery outfall)	(42)
Winter flounder	Coastal MA	0.3% (2/589)	Hep	0 (presumably clean)	(43)
Winter flounder	Narragansett Bay, RI	0.5% (2/414)	Hep	PCBs, metals	(44)
White croaker	Los Angeles, CA	4% (4/100 at 4 stations)	Hep, cholang	PAHs, PCBs, CHIPs	(29)
Starry flounder	San Francisco Bay, CA	1.3% (1/79)	Not stated	PAHs, PCBs, CHIPs	(17)
Winter flounder	Quincy Bay, MA	23% (23/100)	Hep, cholang, mixed	PAHs, PCBs, CHIPs in sediment, liver	(45)
White sucker	Lake Ontario, NY	Up to 6.5% NNS	Hep, cholang	?	(46)

<sup>a</sup>A partial listing, based on publications to date, including gray literature and abstracts. For additional information, including data on neoplasms at other organ sites, see Harshbarger and Clark (73).

<sup>b</sup>Cholang cholangiocellular neoplasms, all variants. Abbreviations: Hep, hepatocellular neoplasms, all variants; NNS, number not stated; PAHs, polynuclear aromatic hydrocarbons; CHIPs, chlorinated hydrocarbon insecticides and pesticides; PCBs, polychlorinated biphenyls.

<sup>c</sup>Indicates species is not strictly a bottom-feeder.

liver neoplasms in feral fishes.

The initial discovery in 1963 of hepatic neoplasms in feral bottom-feeding fishes (23) was perhaps more fortuitous than insightful, but the clues that motivated that field reconnaissance were clear at the time. They were: the epidemics of diet-related liver neoplasms in hatchery-raised rainbow trout, first reported in the spring of 1960 (47) and subsequently shown to be caused by aflatoxins; the publication of Rachel Carson's *Silent Spring* in 1962 (48), chronicling the wide spread of xenobiotic chemicals, particularly insecticides and other pesticides, in aquatic environments; and the report by Halver et al. (49) in 1962 that hepatomas had been induced in rainbow trout experimentally exposed to DDT through the diet (50). In 1963 it had not yet been shown that chlorinated pesticide hydrocarbons adsorb avidly to sedimentary particulates, although it had been found that carcinogenic aromatic hydrocarbons were present in some surface waters and bottom sediments (51,52).

By 1969 it was recognized that organochlorine pesticides do adsorb to particulates, especially to high-organic muck soils (53), and the postulate had already been made that bottom-feeding fishes might be useful as indicators of carcinogens in aquatic environments (23). That DDT is carcinogenic in mice was not reported until 1969 (54,55), seven years after Halver's first report of DDT's hepatocarcinogenicity in trout (49), and 2 years after his second report to that effect (50).

In any case, the effort to affirm the bottom-feeder postulate was abetted in 1970 by the International Union Against Cancer (56), which provided support for meetings (but not for laboratory or field work) of a Task Force on Comparative Oncology and Environmental Carcinogens, most of whose members were already engaged in field surveys of aquatic animals at a reconnoitering level. This is not the place to recount the history of the UICC Task Force [see (7,56,57)], but it needs to be said that, in fact, the Task Force was only partially successful, during its incumbency, in demonstrating some degree of validity in its working hypothesis. Subsequent to the Task Force's demise in 1976, however, it experienced the belated satisfaction of seeing some of its former members and their associates, together with many other investigators, go on to demonstrate the three features of enzootic neoplasms in feral fishes listed above (7-11) (Table 1). To a large extent, interest and activity in these endeavors were supported by the Registry of Tumors in Lower Animals at the Smithsonian Institution in Washington, maintained for some 23 years now with funds mainly from the National Cancer Institute [see (58) for brief history of origins of this registry]. The registry, under the direction of John C. Harshbarger, has played a prominent role in the verification, classification, and archiving of neoplasms discovered by a growing number of field workers. In 1983 several investigators of neoplasms in feral fishes presented the existing pathological, epizootiological, and chemical evidence that fishes were being exposed to carcinogens in certain

habitats to the Congressional Subcommittee on Fisheries and Wildlife Conservation and the Environment, chaired by Representative John B. Breaux of Louisiana (59). In 1984 Congressional Bill H.R. 6118, proposing increased investigation of cancers in lower animals and the relationship of these cancers to human cancers was introduced by Michigan's Representative Dennis M. Hertel and four cosponsors (60). In 1985 a similar bill (H.R. 2155), directed more specifically toward investigations of cancer in fishes and wildlife, was introduced by Representative Hertel. Neither of these bills has been acted upon.

The most comprehensive and precise investigation relating neoplasms in feral fishes to environmental pollutants took its start in 1977 (27) from finding liver neoplasms in pleuronectid fishes (flounder, sole) of Puget Sound and the estuarine portions of its tributary rivers (28,29). Over the ensuing decade a series of closely coordinated studies established, beyond question, an association between a) pathologically confirmed high prevalences of liver neoplasms and b) analytical chemical findings of contaminants in bottom sediments and carcinogens or procarcinogens contained in liver and bile of the subject fish. In these studies the necessity for careful coordination of sampling procedures, with pathological analyses and with analytical chemistry and biochemical studies was for the first time recognized and rigorously applied. The major findings that emerged were as follows:

1. Prevalences of liver neoplasms at nine sites in the Puget Sound area ranged as high as 24% in English sole and were elevated to lesser degree in starry flounder and staghorn sculpin. In general, but with minor deviations, the prevalence of liver neoplasms correlated positively with the degree of urbanization/industrialization in the land areas draining to the respective stations and also with the levels of polynuclear aromatic hydrocarbons (PAHs) present in the sediments. Weaker positive correlations, using the Spearman rank correlation method, were found for metals, PCBs, and chlorinated insecticides in the sediments.
2. Metabolically resistant organic chemicals (PCBs, hexachlorobutadienes, and hexachlorobenzene) were found to be strongly bioconcentrated above sediment levels in the muscle and liver of the English sole. On the other hand, metabolically labile compounds such as the PAHs were low in muscle tissue, but their metabolites were at least 20 times higher in bile from fish at the most highly contaminated sites than in bile from fish at the least contaminated sites. PAH-generated free radicals in liver were correspondingly higher in fish from high PAH-contaminated sites. Over 900 organic compounds, of which more than 500 were PAHs, were detected in sediments, and total PAHs in the stomach contents and in the food animals of fishes at the most contaminated sites ranged as high as 84,000 ng/g.

3. Detailed histopathological studies of fish from the nine study stations not only confirmed the higher prevalences of cholangiocellular and hepatocellular neoplasms in fish from the more highly contaminated environments, but also demonstrated the presence of altered hepatocellular foci and cholangiofibrosis, hepatic megalocytosis, and spongiosis hepatitis—lesions that typically accompany frank hepatic neoplasms in rodents experimentally exposed to known hepatocarcinogenic chemicals (62).

Laboratory experiments in which English sole are exposed to selected pollutant compounds are now being conducted by the Puget Sound investigators to determine whether or not these compounds are capable of reproducing the same array of neoplastic and pre-neoplastic lesions seen in the feral populations of the same species. Because of the large number of chemical species involved in the field studies, it seems unlikely that any single type of study, even DNA-carcinogen adduct analysis, will identify soon and with complete finality the causal chemical or complete constellation of chemicals responsible for the neoplasms seen at any particular aquatic site. It remains possible, however, that some form of specific cellular response, such as activation of a specific regulatory gene (oncogene), inactivation of a specific suppressor gene (antioncogene), or some specific gene translocation by a specific chemical, may yet succeed in forging the needed linkage. The evidence at present must be categorized as strongly inferential in type, pointing to one or more of the many contaminants identified. For liver neoplasms in feral fishes, the linkage to xenobiotic contaminants rests on much the same type of evidence as the linkage of lung cancers to cigarette smoking in human populations.

Meanwhile, additional evidence of similar types continues to accumulate. In 1985 Murchelano and Wolke (37) reported hepatic neoplasms in winter flounder in the heavily polluted Boston Harbor (68). Field studies by EPA investigators Gardner and Spruell (45) report a prevalence of hepatic neoplasms in winter flounder from Quincy Bay (a sub-area within greater Boston Harbor) of 23%. Lower prevalences are reported in winter flounder taken from less contaminated sites in Massachusetts Bay (40), Massachusetts coastal waters (43), and Narragansett Bay, RI (44). It is remarkable that not a single hepatic neoplasm has yet been reported among the large number of winter flounder taken from Georges Bank, a clean habitat chosen as a reference site by many New England field investigators.

Before leaving the topic of neoplasms in fishes as indicators of widespread aquatic contamination by chemical carcinogens, another question must be addressed: If, as we know, some chemical carcinogens and promoters can have fetotoxic, teratogenic, and mutagenic effects on developing mammalian embryos, can they have similar effects on the reproductive processes in fishes? A review by Capuzzo et al. (64) answers this question in the affirmative on the basis of empirical

laboratory studies available. At the same time, these authors note that, unfortunately, clear linkage between these laboratory studies and the population declines known in many aquatic species occupying contaminated environments do not exist because fisheries biologists do not now have good methods for distinguishing between population declines caused by reproductive failures and those caused by over-harvesting. Capuzzo et al. have identified an extremely important area for future research. It is not likely that cancers in older fish will cause serious declines in fish populations, but the cancers indicate the presence of chemicals that well might cause reproductive failures. In turn, such failures would affect the nutritional availability of food fishes to human populations, an effect more far-reaching than can be imagined for carcinogenic effects alone.

## Fishes as Conveyors of Carcinogens

Increasingly, as the news media have made widely known the discoveries of enzootics of neoplasia in fishes, the public has been asking whether or not there is increased risk of developing cancer if one eats fish taken from habitats where prevalences of fish neoplasms are high. The specific answer to this question is not known. The question itself has rationality only if one takes into consideration the content of carcinogens in the particular fish that is eaten, the quantity of fish that is eaten, and the particular method of preparation for the table. The simple question subdivides itself into a multitude of questions as large as the number of permutations that can be derived from the almost infinite variations possible within these parameters. Further, many additional variables enter the picture of risk assessment, such as risk values extrapolated from rodent bioassays, assumptions that risk increments for multiple carcinogens in a particular fish population are additive (versus synergistic or antagonistic), and assumptions that the identified and quantified carcinogens in the edible flesh are the only ones actually present. Since no one can vouch for the validity of these and other assumptions inherent in pencil-and-paper (mathematical/extrapolative) risk assessments, one can only conclude that this type of risk assessment is risky business. Or, as former Director of EPA William Ruckelshaus put it: "Risk assessments are like captured spies. If you torture them long enough, you can get them to say anything you want."

An example can be found in the recent risk assessments calculated for persons eating variable quantities of winter flounder, soft-shelled clams, and lobster from Quincy Bay, MA. Calculations based on worst-case assumptions were two or three log increments higher than those for best-case assumptions (65). In the worst-case assessment, a risk increment of one or two cancers per 100 high consumers was found. A similar worst-case risk assessment calculated for high consumers of fish and crabs from Commencement Bay, Puget Sound, WA, came up with an increment of one or two cancers per 15,220 such consumers (66). However, in this cal-

culatation, only the effect of the highest single carcinogen was factored into the equation, while in the Quincy Bay calculations it was assumed the effects of multiple carcinogens would be additive. Two such assessments are not comparable, nor is it possible to know which was the more valid.

A seeming paradox is noteworthy in relation to the Quincy Bay studies (45); it lies in the fact that levels of PAHs were consistently undetectable in the edible muscle of winter flounder, while levels of PAHs ranged from about 40 to 50 ng/g to about 1400 ng/g in lobster muscle and hepatopancreas (tomalley) respectively. Levels in soft-shelled clams approximated those in lobster muscle. Thus it would seem that, while winter flounder are more important as indicators of environmental carcinogens (liver tumors in 23% versus 0 tumors in clams and lobster), the crustaceans and molluscs are more important as accumulators and conveyors of the PAH carcinogens. The paradox is resolved if we consider that the flounder liver transforms and eliminates most of the PAH carcinogens (67) and, moreover, that humans do not eat flounder liver or bile. Thus, humans may be protected by the interposition of a flounder liver barrier between human consumers and the invertebrates on which the flounder feed. This is not true for marine birds and mammals that ingest fishes whole (68), nor is it true for carcinogens that are not metabolized in liver, unlike PAHs.

Other methods of risk assessment are available, each with its own advantages and disadvantages. For example, to avoid the assumptions that the carcinogens identified in edible fish flesh are the only ones present and that the increments for multiple carcinogens are additive, one can start from data obtained from the activity of extracts of the flesh in bacterial mutagenesis tests, cell culture tests for DNA repair, cell culture transformation tests, or tests for loss of gap junctions in cell cultures. Or one can perform rodent bioassays in direct feeding experiments using the contaminated fish or shellfish as the protein moiety of the diet. Or one can carry out epidemiological studies on human subjects who are high consumers of fish taken from either high liver-cancer populations or from high carcinogen-containing populations. The epidemiological approach is probably the most valid, but is very expensive, difficult of design, and requires time elements that may render the findings soon obsolete in the face of changing patterns of chemical contamination of aquatic environments. At least two epidemiological studies have actually been undertaken and are still in progress (69,70). The results with respect to cancer risks are not yet in. Potential problems relating to aquatic foods as conveyors of carcinogens are complex, but deserve continued, thoughtful attention.

## The Future

What will the next century bring in the form of information and actions concerned with the interrelationships between aquatic animal health and human health?

Obviously it would be unwise to attempt detailed predictions involving extremely complex biological systems affected by global variables in inputs of cytotoxic and genotoxic chemicals and radionuclides. Much depends upon socio-politico-economic factors that ultimately determine and regulate our responses to environmental degradation. Three trends seem clearly established: a) Stocks of feral fishes are being depleted. Some formerly abundant species such as the Pacific anchovy and sardine have virtually completely disappeared. Other species, such as Atlantic herring, haddock, cod, and many others are severely depopulated, ostensibly because of over-harvesting, but possibly also because of reproductive failures related to degraded habitats. b) In some parts of the U.S. and other industrialized countries, the availability of feral fishes for consumption has already been curtailed because of concern (only partially justified on the basis of data) that contaminants in the flesh may be injurious to consumers. c) Fish farming and mollusk farming (aquaculture) is on the rise as a compensatory response on the part of commercial interests.

It has been estimated that the world population of *Homo sapiens* will reach and, for some time, hold at a maximum level in 162 years, give or take 50 years. If this happens, it is probable that within the next century mankind's priorities and policies for global environmental preservation and/or management will largely be determined. In that time, a decision may be forced either by default or by positive choice regarding two major options: to reverse current trends permitting massive environmental degradation and thus to preserve some level of planetary homeostasis sufficient to sustain diversity of species and high levels of human population within the context of recently past millennia (i.e., to remain in the womb of mother earth, so to speak); or to abandon serious attempts to preserve a relatively steady state of planetary homeostasis and move toward a mankind-controlled synthetic environment and an autotrophic or semiautotrophic existence, defined almost entirely by human technological devices (i.e., to cut the umbilical cord). Of such stuff are science fiction novels made. But either way, huge changes in technology will be necessary.

Most ecologists will agree we are not prepared to follow the second course. Even if we are to go the second route, there can be no question that, as in organic (Darwinian) evolution, the old engine must be kept running at the same time that new blueprints are drawn and parts of the new engine are prepared to go into strategic places through the process of cultural evolution (epievolution). In pragmatic terms, we will know that earth's people can make such a huge step in punctuated cultural evolution when a successful semiclosed-system, self-replicable human habitation module has been set up, suitable for colonization of some other planet or moon similar to earth in its elementary composition, but devoid of higher life forms. Until then, we will do well to preserve the *homeostasis quo*. It would be ironic and

perhaps poetically just, if mankind were to construct such a module only in time to survive as a species on the planet we already occupy.

The development of the following attitudes and activities in relation to preserving useable resources of aquatic foods in the immediate future are foreseeable:

1. The attitude will be adopted that reversal or at least retardation of present trends toward degradation of major environmental components is a matter of population sustenance. These degraded components involve not only the loss of productive aquatic habitats, but also the processes of deforestation, carbon dioxide increase, acidification of rainfall, toxic air pollution, ozone depletion, oxygen depletion, eutrophication, desertification, soil erosion, and rises in ocean levels — all of which have impacts on each other. The components at stake are equivalent to the vital organs of the planet, and the loss, through disease, of one component can lead to the loss of the organism Earth for purposes of human survival at high population levels.

With particular respect to aquatic food resources, it will become more widely recognized that the chief immediate threat is a combination of over-harvesting and contamination of habitats with toxic anthropogenic substances. The effects of this multitude of toxins on the reproductive capacity of aquatic food webs is probably of far greater import than the impact on survival of adult fishes; but this is not scientifically established. Therefore, research aimed toward establishing a connection between habitat contamination and reproductive failures deserves high priority in the immediate future.

2. We are only on the edge of a period during which it will be determined whether fishes and other aquatic food sources are important conveyors of carcinogens and other toxic substances to human consumers. Epidemiological studies have already reported serious effects on fetal and infant health related to the high consumption of PCB-contaminated fish before and during pregnancy (69,70). These effects are comparable to those of smoking cigarettes during pregnancy. PCBs are transferred from mother to fetus and child via the placenta and milk. Swain has calculated that 5 generations would be required to void, eventually, a succession of female first-born descendants of a PCB burden originating in the founder mother, without any additional input of PCBs during those 5 generations (71). The implications of this pattern in the pharmacokinetics of PCBs are especially serious in view of recent papers by McKinney and coworkers (72,73) who observe that PCBs and congeners have the potential, on the basis of structural properties shared with thyroid hormones, to cause hypothyroidism through competitive binding with thyroid hormone carrier proteins and recep-

tors. If these workers are correct, we have an attractive explanation for the heretofore enigmatic finding of high prevalences of thyroid hyperplasia in coho salmon in the Great Lakes, where these fish carry high body burdens of PCBs (74,75).

As already stated, we are still poorly informed on the role of fishes and shellfishes as conveyors of carcinogens/promoters to consumers. This question will capture the attention of investigators and public health professionals in the U.S. and other affluent nations, where the word "cancer" triggers strong emotional responses. In countries such as Ethiopia and Sudan, prospects of mass starvation make dietary cancers a luxury the populace there would like to live long enough to experience. If and when more equitable distribution of foods is achieved globally, effects of fish-conveyed carcinogens will assume more world-wide importance, but will probably be overshadowed by the effects of toxic substances on reproductive capacities of fishes and human beings alike. In the meantime, total and selected types of cancer incidences are on the rise in the U.S. (76), and reproductive rates are declining in some ethnic and racial groups but rising in others. As suggested by Miller (12), it would be a wise policy to take a hint from an old Japanese tradition by setting up banks for storing and periodically analyzing umbilical cords and placentas, which are available in large quantity without requiring invasive procedures.

3. Monitoring of aquatic foods will increase, although there will be dramatic changes in the kinds and methods of monitoring. At present the National Oceanic and Atmospheric Administration (NOAA), the Food and Drug Administration (FDA), the National Institute of Environmental Health Sciences (NIEHS), and the U.S. Environmental Protection Agency (EPA) share, in a complex interrelationship, the responsibility for protecting consumers from contaminated aquatic foods. Largely because it has the equipment and technology for sampling marine environments, NOAA, through two of its arms, the National Marine Fisheries Service (NMFS) and the National Ocean Service (NOS), has made the greatest contributions toward identifying the locations of chemically contaminated aquatic animals and the effects of the contaminants on those animals. NMFS through its National Status and Trends Program (NS and T Program), operative for more than 20 years, has played the key role in demonstrating declines in fish stocks. NOS, within the NS and T Program and through its Benthic Surveillance Program, collects bottom feeding fish, shellfish, and sediments and analyzes them for toxic metals, organic chemicals, metabolites of aromatic hydrocarbons, and fish diseases. It was largely through these activities that liver neoplasms in bottom feeding fishes of our East and



West Coast estuaries were discovered and correlated with high levels of sediment contaminants.

It seems prudent that, in the future, the Benthic Surveillance Program of NOS be intensified and coordinated more closely with FDA's seafood testing activities. The "Market Basket" testing as now performed by the FDA is virtually worthless so far as identification of contaminated habitats is concerned, and has little value in protecting consumers. Capuzzo and collaborators (18) estimate that the FDA tested less than 0.001% of the fish consumed in 1982 for chemical contamination. In the future, consumers (particularly females of prechild-bearing and child-bearing ages) deserve to know where the seafoods they buy come from, and what contaminants are present in samples from the species harvested from those areas. It is accordingly of equal or greater importance to identify *clean* fishery habitats as it is to identify contaminated habitats and contaminated animals. In the past the focus has been almost entirely on habitats suspected of being contaminated. The options of consumers need concrete definition in terms of the nature and quantities of specific contaminants. Some consumers have already indicated a willingness to trade off the risk of eating carcinogen/promoter-containing fish in exchange for the positive benefits of receiving Omega-3 fatty acids from the same fish (71).

The attitude that oceans and waterways are proper and safe places for dumping domestic and industrial wastes is anathema both for fish health and for human health. New York and New Jersey have been carrying out a recently adopted policy of dumping sewage sludge at a site slightly beyond the coastal shelf drop-off, 106 miles east of the shoreline and 100 miles beyond the former dump site off Sandy Hook. Commercial fishermen are already alleging damage to fish and crustaceans being harvested near the new dump site, but these allegations have not been confirmed or refuted scientifically, because no scientific investigation has yet been conducted.

In response to public demands to clean up Boston Harbor, the Massachusetts Water Resources Authority is planning to discharge secondary sewage effluents at a site 8 miles outside Boston Harbor. Only approximately 50% of the total toxics (varying widely within the complex mixture) from the raw sewage will have been removed from this effluent of  $500 \times 10^6$  (and growing) gallons daily. The terminal portion of the discharge conduit is designed to diffuse the outflow into Massachusetts Bay, assuring more immediate dilution of the sewage and more immediate dispersal of the toxics into waters not far from Georges Bank—until now a highly productive and clean fishing ground.

In Southern California a similar longer sewage pipeline has been discharging at a deep water site

off the Pacific coastal shelf for some years. This policy of extending pipelines further and further out is tantamount to the policy of sending air pollution elsewhere faster by building taller smokestacks. It alleviates local contamination by effecting more rapid global dissemination and, eventually, more rapid global build-up of contaminants. It may be remembered that tritium fallout from nuclear weapons tests in the Pacific in the 1940s through 1960s was transported via aqueous routes to the eastern Atlantic in as little as 10 years.

The solution to the general problem of disposal of hazardous wastes is intuitively recognized by ecologists and by most of the lay public as well. It is not to dispose of wastes by transporting them elsewhere in the traditional way, but to recover and contain them, to re-separate and recycle the useful components, and to transform the remainder to harmless compounds that will not perturb environmental homeostasis. Even radionuclides can be separated and recycled under containment conditions. We suffer from a multitude of technologies that J. A. Couch aptly characterizes (personal communication) as "incomplete technologies." Such technologies can be made complete and tolerable only when their waste products are recycled or converted to compounds nondegrading to ecosystems. It is said the price for this will be astronomical; but to continue the metaphor, what price would not be small for a living planet? An optimist's guess is that as scientists (including biologists), engineers, technologists, and business people become increasingly aware that there are economic niches to be found in garbage, sewage, and hazardous waste redeployment (not disposal as it is now generally conceived), there will be no shortage of innovations in technology. These innovations should be taking place even while the stop-gap procedures of extending pipelines into the oceans are taking place. In the main, academia is the proper and most likely place for these innovations to be conceived. A few universities are already offering curricula including such technology, and others will surely honor the point of these path setters. We are about to see the blossoming of disciplines in ecopathology and ecotherapeutics, branches now budding from the mainstem of the classical ecological science that sprang to life in the century nearly past.

In the century to come and for many centuries thereafter, we will surely see a continued constructive response to the understandably disheartened Albert Schweitzer who, in an uncharacteristic moment of despair, perceived that: "Man has lost the capacity to foresee and to forestall. He will end by destroying the earth" (48). There will be many to rise to the challenge implicit in Dr. Schweitzer's statements.

Will the new caretakers be able to muster the societal and scientific *animus* needed to prevail? Human society and the sciences that are part of it have no other choice. As long as water is a solvent on which life processes depend, and as long as water is a major vehicle for the transport of substances throughout the planet, the



interrelated communities of aquatic organisms will be sensitive indicators of the integrity of earth's ecosystems. It is a self-evident truism that when aquatic animal populations experience ill health from exposure to anthropogenic chemicals, human health is in jeopardy as well.

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## REFERENCES

- Kimura, I. Aquatic pollution problems in Japan. *Aquat. Tox.* 11: 287-301 (1988).
- Warren, K. S., and Bowers, J. Z., Eds. *Parasitology. A Global Perspective*. Springer-Verlag, New York, 1983.
- Halstead, B. W. Poisonous and venomous marine animals of the world, Vol. 2. U.S. Government Printing Office, Washington, DC, 1967, pp. 679-902.
- Ray, S. M. Paralytic shellfish poisoning: a status report. In: *Current Topics in Comparative Pathobiology* (T. C. Cheng, Ed.), Academic Press, New York, 1971, pp. 171-200.
- Prakash, A. Dinoflagellate blooms—an overview. In: *First International Congress on Toxic Dinoflagellate Blooms*, Massachusetts Science and Technology Foundation, Wakefield, MA, 1975, pp. 1-6.
- Anderson, D. M., White, A. W., and Baden, D. G. (Eds.). *Toxic dinoflagellates. Proceedings of the Third International Conference on Toxic Dinoflagellates*, Elsevier, New York, 1985.
- Dawe, C. J., Scarpelli, D. G., and Wellings, S. F. (Eds.). *Tumors in aquatic animals. In: Progress in Experimental Tumor Research*, Vol. 20. S. Karger, Basel, Switzerland, 1976.
- Kraybill, H. F. Dawe, C. J., Harshbarger, J. C., and Tardiff, R. G. Eds. *Aquatic Pollutants and Biologic Effects, with Emphasis on Neoplasia*. Ann. N.Y. Acad. Sci. 298 (1977).
- Dawe, C. J., Harshbarger, J. C., Kondo, S., Sugimura, T., and Takayama, S. (Eds.). *Phyletic approaches to cancer*. In: *Proceedings of the 11th International Symposium of the Princess Takamatsu Cancer Research Fund*, Tokyo, 1980. Japan Scientific Societies Press, Tokyo, 1981.
- Pritchard, J. B., and Miller, D. S. Introduction: the comparative approach to mechanisms of pollutant toxicity. *Environ. Health Perspect.* 71: 3-4 (1987).
- Malins, D. C., and Jensen, A. Eds. *Aquat. Toxicol.* 11 (1988).
- Miller, R. W. Health implications of water contaminants in man. Ann. N.Y. Acad. Sci. 298: 557-560 (1977).
- Farrington, J., Goldberg, E., Risebrough, R., Martin, J., and Bowen, V. U.S. "Mussel Watch" 1967-1978: an overview of the trace metal, DDE, PCB, hydrocarbon and artificial radionuclide data. *Environ. Sci. Technol.* 17: 490-496 (1983).
- Friberg, L. The GESAMP evaluation of potentially harmful substances in fish and other seafood with special reference to carcinogenic substances. *Aquat. Toxicol.* 11: 379-393 (1988).
- Pearce, J. B., and Despres-Patanjo, L. A review of monitoring strategies and assessments of estuarine pollution. *Aquat. Toxicol.* 11: 323-343 (1988).
- O'Connor, J. M., and Huggett, R. J. Aquatic pollution problems, North Atlantic coast, including Chesapeake Bay. *Aquat. Toxicol.* 11: 163-190 (1988).
- McCain, B. B., Brown, D. W., Krahn, M. M., Myers, M. S., Clark, R. C., Jr., Chan, S.-L., and Malins, D. C. Marine pollution problems, North American West Coast. *Aquat. Toxicol.* 11: 143-162 (1988).
- Capuzzo, J. M., McElroy, A., and Wallace, G. Fish and Shellfish Contamination in New England Waters: An Evaluation and Review of Available Data on the Distribution of Chemical Contaminants. Report of the Woods Hole Oceanographic Institution and the University of Massachusetts Environmental Science Program, 1987, 59 pp.
- Lucké, B., and Schlumberger, H. G. Transplantable epitheliomas of the lip and mouth of catfish. I. Pathology. Transplantation to anterior chamber of eye and into cornea. *J. Exper. Med.* 74: 397-408 (1941).
- Schlumberger, H. G. Tumors characteristic for certain animal species. A review. *Cancer Res.* 17: 823-832 (1957).
- Russell, R. E., and Kotin, P. Squamous papilloma in the white croaker. *J. Natl. Cancer Inst.* 18: 857-861 (1957).
- Mix, M. S. Cancerous diseases in aquatic animals and their association with environmental pollutants: a critical literature review. *Marine Environ. Res.* 20: 1-136 (1986).
- Dawe, C. J., Stanton, M. F., and Schwartz, F. J. Hepatic neoplasms in native bottom-feeding fish of Deep Creek Lake, Maryland. *Cancer Res.* 24: 1194-1201 (1964).
- Dawe, C. J., Sonstegard, R., Stanton, M. F., Woronecki, D. E., and Reppert, R. T. Intrahepatic biliary duct neoplasms in *Catostomus commersoni*. *Prog. Exp. Tumor Res.* 20: 195-204 (1976).
- Brown, E. R., Hazdra, J. J., Keith, L., Greenspan, I., Kwapinski, J., and Beamer, P. Frequency of fish tumors found in a polluted watershed as compared to nonpolluted Canadian waters. *Cancer Res.* 33: 189-198 (1973).
- Brown, E. R., Sinclair, T., Keith, L., Beamer, P., Hazdra, J. J., Nair, V., and Callaghan, O. Chemical pollutants in relation to diseases in fish. *Ann. N.Y. Acad. Sci.* 298: 535-546 (1977).
- McCain, B. B., Pierce, K. V., Wellings, S. R., and Miller, B. S. Hepatomas in marine fish from an estuary. *Bull. Environ. Contam. Toxicol.* 18: 1-2 (1977).
- Malins, D. C., McCain, B. B., Myers, M. S., Brown, D. W., Krahn, M. M., Roubal, W. T., Schiewe, M. H., Landahl, T. T., and Chan, S.-L. Field and laboratory studies of the etiology of liver neoplasms in marine fish from Puget Sound. *Environ. Health Perspect.* 71: 5-16 (1987).
- Malins, D. C., McCain, B. B., Landahl, J. T., Myers, M. S., Krahn, M. M., Brown, D. W., Chan, S.-L., and Roubal, W. T. Neoplastic and other diseases in fish in relation to toxic chemicals: an overview. *Aquat. Toxicol.* 11: 43-67 (1988).
- Smith, C. M., Peck, T. H., Klauda, R. J., and McLaren, J. B. Hepatomas in Atlantic tomcod *Microgadus tomcod* (Walbaum) collected in the Hudson River estuary in New York. *J. Fish Dis.* 2: 313-319 (1979).
- Klauda, R. J., Peck, T. H., and Rice, G. K. Accumulation of polychlorinated biphenyls in Atlantic tomcod (*Microgadus tomcod*) collected from the Hudson River estuary in New York. *Bull. Environ. Contam. Toxicol.* 27: 829-835 (1981).
- Baumann, P. C., Smith, W. D., and Ribick, M. Hepatic tumor rates and polynuclear aromatic hydrocarbon levels in two populations of brown bullheads (*Ictalurus nebulosus*). In: *Polynuclear Aromatic Hydrocarbon* (M. W. Cooke, A. J. Dennis, and G. L. Fisher, Eds.), Battelle Press, Columbus, OH, 1982, pp. 93-102.
- Baumann, P. C., and Harshbarger, J. C. Frequencies of liver neoplasia in a feral fish population and associated carcinogens. *Marine Environ. Res.* 17: 324-327 (1985).
- Black, J. J., Evans, E. D., Harshbarger, J. C., and Zeigel, R. F. Epizootic neoplasms in fishes from a lake polluted by copper mining wastes. *J. Natl. Cancer Inst.* 69: 915-926 (1982).
- Black, J. J. Field and laboratory studies of environmental carcinogenesis in Niagara River fish. *J. Great Lakes Res.* 9: 326-334 (1983).
- Black, J. J., Fox, H., Black, P., and Bock, F. Carcinogenic effects of river sediment extracts in fish and mice. In: *Water Chlorination Chemistry, Environmental Impact and Health Effects*, Vol. 5 (L. R. Jolly et al., Eds.) Lewis Publishing, Chelsea, MI, 1985.
- Murchelano, R. A., and Wolke, R. E. Epizootic carcinoma in the winter flounder, *Pseudopleuronectes americanus*. *Science* 228: 587-589 (1985).
- Boehm, P. D., Steinhauer, W., and Brown, J. Organic pollutant biogeochemistry studies, Northeastern U.S. marine environment. Battelle, New England, Marine Res. Lab. Final Report, Contribution No. NA-83-FA-C-00022, to National Oceanic and

- Atmospheric Administration, National Marine Fisheries Service, Highlands, NJ, 1984, 61 pp.
39. Zdanowicz, U. S. Gadbois, D. F., and Newman, M. W. Levels of organic and inorganic contaminants in sediments and fish tissues and prevalences of pathological disorders in winter flounder from estuaries of the Northeast United States, 1984. Oceans '86 Conference Record: The Institute of Electrical and Electronics Engineers, Piscataway, NJ, 1986, pp. 1-8.
  40. Dawe, C. J. Survey of pathology of winter flounder (*Pseudopleuronectes americanus*) in Salem Harbor, MA. In: Project Report, SESD Project, Edgerton Research Laboratory, New England Aquarium, Boston, MA, 1986, pp. 107-111.
  41. May, E. B., Lukovic, R., King, H., and Lipsky, M. M. Hyperplastic and neoplastic alterations in the livers of white perch (*Morone americana*) from the Chesapeake Bay. J. Natl. Cancer Inst. 79: 137-143 (1987).
  42. Thiagarajah, A., Bender, M. E., and Greaves, J. Pancreatic and hepatic neoplasms in oyster toadfish, *Opsanus tau*. (Abstract) In: Fourth International Symposium on Responses of Marine Organisms to Pollutants (J. J. Stegeman and J. M. Capuzzo, Eds.), Woods Hole Oceanographic Institute, Woods Hole, MA, 1987.
  43. Sass, S. L., and Murchelano, R. A. Hepatic tumors and other liver pathology in Massachusetts flatfish. Aquat. Toxicol. 11: 421-422 (1988).
  44. Lee, T. C., Saila, S. B., and Wolke, R. E. Winter Flounder Contaminant and Pathological Survey—Narragansett Bay and Vicinity. Draft Final Report, University of Rhode Island, RI 1988, 63 pp.
  45. Gardner, G. R., and Spruell, R. J. A Histopathological and Chemical Assessment of Winter Flounder, Lobster, and Soft-Shell Clam Indigenous to Quincy Bay, Boston Harbor and An *In Situ* Evaluation of Oysters Including Sediment (Surface and Cores) Chemistry. A Report Prepared by the U.S. Environmental Protection Agency, Environmental Research Laboratory, Narragansett, RI, 1988.
  46. Cairns, V. W., and Fitzsimmons, J. D. The occurrence of epidermal papillomas and liver neoplasms in white suckers, *Catostomus commersoni*, from Lake Ontario. In: Proceedings of the 14th Annual Aquatic Toxicity Workshop (A. J. Niimi and K. R. Solomon, Eds.), Canadian Technical Report of Fisheries and Aquatic Sciences. No. 1607. Department of Fisheries and Oceans, Bayfield Institute, Burlington, Ontario, Canada, 1988.
  47. Goldblatt, L. A. Chapter I, Introduction. In: Aflatoxin, Scientific Background, Control, and Implications (L. A. Goldblatt, Ed.), Academic Press, New York, 1969, pp. 1-11.
  48. Carson, R. Silent Spring. Fawcett Crest, New York, 1962, 304 pp.
  49. Halver, J. E. In: A Summary of Research Progress on Trout Hepatoma (H. F. Kraybill, Ed.), Office of Field Studies, National Cancer Institute, 1962.
  50. Halver, J. E. Aflatoxicosis and trout hepatoma, Chapter X. In: Scientific Background, Control, and Implications (L. A. Goldblatt, Ed.), Academic Press, New York, 1969, pp. 265-306.
  51. Borneff, J., and Fisher, R. Kanzerogene Substanzen in Wasser und Boden. VII. Untersuchungen an filter-aktivkohle nach Verwendung im Wasserwerke. Arch. Hyg. u. Bakt. 146: 1-16 (1962).
  52. Borneff, J., and Fisher, R. Kanzerogene Substanzen in Wasser und Boden. XII. Polyzyklische, aromatische Kohlenwasserstoffe in Oberflächenwasser. Arch. Hyg. u. Bakt. 146: 572-585 (1962).
  53. Lichtenstein, E. P. Pesticide residues in soils, water, and crops. Ann. N.Y. Acad. Sci. 160: 155-161 (1969).
  54. Innes, J. R. M., Ulland, B. M., Valerio, M. G., Petrucelli, L., Fishbein, L., Hart, E. R., Palletta, A. J., Bates, R. R., Falk, H. L., Gart, J. J., Klein, M., Mitchell, I., and Peters, J. Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: a preliminary note. J. Natl. Cancer Inst. 42: 1101-1114 (1969).
  55. Turusov, V. S., Day, N. E., Tomatis, L., Gati, E., and Charles, R. T. Tumors in CF-1 mice exposed for six consecutive generations to DDT. J. Natl. Cancer Inst. 51: 983-997 (1973).
  56. Dawe, C. J. Comparative oncology and environmental carcinogens. Union Int. Contre Cancer Bull. Vol. 8, No. 4: 2-3 (1970).
  57. Dawe, C. J. Neoplasms in aquatic animals as indicators of environmental carcinogens. Union Int. Contre Cancer Bull. Vol. 13, No. 2: 5 (1975).
  58. Harshbarger, J. C. The Registry of Tumors in Lower Animals. Natl. Cancer Inst. Monogr. 31: xi-xvi (1969).
  59. Breaux, J. B. Fish Cancer Epidemics Oversight. Hearing before the Subcommittee on Fisheries and Wildlife Conservation and the Environment, of the Committee on Merchant Marine and Fisheries. House of Representatives. First Session on The Causes of Reported Epidemics of Cancer in Fish and the Relationship between their Occurrence and Environmental Quality and Human Health. Sept. 21, 1983. Serial No. 98-40, U.S. Government Printing Office, Washington, DC, 1984.
  60. Hertel, D. M. H. R. 6118 to require that a comprehensive study be prepared regarding the present status of lower animal cancer research at State and Federal levels, and means for improving and coordinating that research. 98th Congress, second session, 1984.
  61. Hertel, D. M. H. R. 2155 to require that a comprehensive study be prepared regarding the present status of fish and wildlife cancer research at the State and Federal levels and means for improving and coordinating that research. 99th Congress, first session, 1985.
  62. Myers, M. S., Rhodes, L. D., and McCain, B. B. Pathologic anatomy and patterns of hepatic neoplasms, putative preneoplastic lesions, and other idiopathic conditions in English sole (*Parophrys vetulus*) from the Duwamish River estuary, Seattle, Washington. J. Natl. Cancer Inst. 78: 333-363 (1987).
  63. Murchelano, R. A. Fish health and environmental health. Environ. Health Perspect. 86: 257-59 (1990).
  64. Capuzzo, J. M., Moore, M. N., and Widdows, J. Effects of toxic chemicals in the marine environment: predictions of impacts from laboratory studies. Aquat. Toxicol. 11: 303-311 (1988).
  65. Reimold, R. J., Bysshe, S. E., Cooper, C. B., Doyle, M., and Garcia, M. Analysis of Risks from Consumption of Quincy Bay Fish and Shellfish. Task IV Report prepared for U.S. Environmental Protection Agency, Region I. May, 1988. 69 pp. and 3 appendices, 66 pp.
  66. Versar, Inc. Final Report: Risk Assessment of Human Health Risk from Ingesting Fish and Crabs from Commencement Bay. Report under contract No. 68-03-3149 to the U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response, 1985.
  67. Varanasi, U., and Gmur, D. J. Hydrocarbons and metabolites in English sole (*Parophrys vetulus*) exposed simultaneously to (<sup>3</sup>H) benzo(a)pyrene and (<sup>14</sup>C) naphthalene in oil-contaminated sediment. Aquat. Toxicol. 1: 49-67 (1981).
  68. Peakall, D. B., and Fox, G. A. Toxicological investigations of pollutant-related effects in Great Lakes gulls. Environ. Health Perspect. 71: 187-193 (1987).
  69. Jacobson, S. W., Jacobson, P. M., Schwartz, P. M., and Fein, G. G. Intrauterine exposure of human newborns to PCBs: measures of exposure. In: PCBs: Human and Environmental Hazards (F. M. D'itri and M. A. Kamrin, Eds.), Butterworth Publishers, Boston, MA 1983, pp. 311-343.
  70. Humphrey, H. E. B. Population studies of PCBs in Michigan residents. In: PCBs: Human and Environmental Hazards (F. M. D'itri and M. A. Kamrin, Eds.), Butterworth Publishers, Boston, MA 1983, pp. 299-310.
  71. Swain, W. R. Human health consequences of consumption of fish contaminated with organochlorine compounds. Aquat. Toxicol. 11: 357-377 (1988).
  72. McKinney, J. D. Do residue levels of polychlorinated biphenyls (PCBs) in human blood produce mild hypothyroidism? J. Theor. Biol. 129: 231-241 (1987).
  73. Chae, K., and McKinney, J. D. Molecular complexes of thyroid hormone tyrosyl rings with aromatic donors. Possible relationship to receptor protein interactions. J. Med. Chem. 357-362 (1988).
  74. Leatherland, J. F., and Sonstegard, R. A. Thyroid dysfunction in Great Lakes coho salmon *Oncorhynchus kisutch* (Walbaum); seasonal and intake differences in serum T<sub>3</sub> uptake and serum total and free T<sub>4</sub> and T<sub>3</sub> levels. J. Fish Dis. 4: 413-423 (1981).

- 75. Leatherland, J. F. Endocrine factors affecting thyroid economy of teleost fish. *Am. Zool.* (in press).
- 76. Anonymous. New cancer statistics released J. Natl. Cancer Inst. 80: 8 (1988).
- 77. Hersey, J. Blues. Alfred A. Knopf, New York, 1987, p. 168.
- 78. Harshbarger, J. C., and Clark, J. B. *Sci. Tot. Environ.*, in press.